REMARKS

Claims 1-19, 21-23 and 26-29 are pending. By this Amendment, no claims are cancelled, independent claims 1 and 27 are amended, and no new claims are added. Support for this Amendment can be found in the specification as originally filed, and no new matter is believed to be introduced.

Claim Rejections – 35 U.S.C. § 102(b)

The Final Office Action mailed June 29, 2011 (hereinafter the "June 29, 2011 Office Action") rejected claims 1, 3-7, 10-19, 21, 22-23, 26-29 under 35 U.S.C. 102(b) as being anticipated by CA 02385302 A1 to Akira et al. Applicants respectfully traverse these rejections, as a *prima facie* case of anticipation has not been established at least for the reason that Akira et al. fails to disclose, teach or suggest all claim limitations. In an effort to advance prosecution, Applicants also amend independent claims 1 and 27 to further clarify the presently claimed invention.

Independent Claims 1 and 27

Independent claim 1 of the presently claimed invention is directed to a method of separating and/or enriching prokaryotic DNA in vitro, comprising the steps of (a) contacting at least one prokaryotic DNA, present in solution, with a protein which specifically binds prokaryotic DNA and has 25% to 35% homology with the wild type CGBP protein, thereby forming a protein-DNA complex, and (b) separating said complex. Following the presently claimed method, non-methylated DNA is separated from methylated DNA and simultaneously

enriched when the wild type CGBP protein specifically binds prokaryotic DNA, which allows for further analysis.

Independent claim 27 of the presently claimed invention as amended is directed to a method of separating and/or enriching non-methylated DNA from a mixture of non-methylated and methylated DNA in vitro comprising: providing a mixture containing at least one non-methylated DNA and at least one methylated DNA, contacting the mixture in a solution with a protein having between about 25% and 35% homology with a wild type CGBP protein to specifically bind the protein and the at least one non-methylated DNA, thereby forming a protein-DNA complex, and separating the complex, such that the protein does not specifically bind to the at least one methylated DNA.

In stark contrast to the presently claimed inventions of independent claims 1 and 27, which both have the limitation of a protein which has 25% to 35% homology of the wild type CGBP protein, Akira et al. is directed entirely to TLR9. (*See, e.g.*, Specification, p. 2 at ¶ 3 ("The goal of the present invention is to provide a receptor protein TLR9...the DNA encoding it..."); Claim 1.) The June 29, 2011 Office Action fails to cite with any particularity where this claimed protein (25% to 35% homology of the wild type CGBP protein) is disclosed, taught or even suggested. Indeed, this claimed protein version of the wild type CPGB protein is a completely different protein than the one used in Akira et al., not to mention the completely different objects of providing the respective proteins. Considering the complete disconnect between the presently claimed invention and the subject matter disclosed in Akira et al., Applicants respectfully submit the June 29, 2011 fails to teach, disclose or suggest all claim limitations of the presently claimed invention.

More specifically, in rejecting independent claims 1 and 27, the June 29, 2011 cited the abstract, claim 23 on page 27, paragraphs 2-3 on page 10, paragraph 1 on page 11, paragraphs 1-2 on page 18, and lines 1-17 on page 19. As provided in more detail below, Applicants interpretation of these sections provides that Akira et al. is directed to the protein TLR9 which is capable of recognizing bacterial DNA having non-methylated CpG sequences, as well as a mouse model for the screening for antagonists and agonists of TLR9, wherein the TLR9 activiety is determined in vivo, and further a kit for diagnosing diseases related to the deletion, substitution and/or addition in the TLR9 sequence of an individual, the kit comprising the DNA sequence of wt TLR9 for comparison with the possible altered TLR9 sequence.

Indeed, when Akira et al. is considered in its entirety, it is clear that "[t]he goal of the present invention [in Akira et al.] is to provide a receptor protein TLR9...the DNA encoding it..." (*See, e.g.*, Akira et al. at page 2 at ¶ 2; *see also* page 7 at ¶¶ 2-3 (directed at TLR9); Examples on pages 20-25; and Industrial Applicability on page 25.)

Claim 23 of Akira et. refers to a screening method for an agonist or an antagonist of a receptor protein (TLR9 being the disclosed receptor protein), comprising culturing a cell expressing the receptor protein (TLR9) in the presence of a target substance (i.e., agonist or antagonist) and evaluating the receptor protein (TLR9) activity in the cell.

Page 10, paragraph 2, of Akira et al. discusses carrying out a functional analysis of the receptor protein (TLR9) specifically recognizing bacterial DNA having the unmethylated CpG sequence by using fusion proteins obtained by fusing proteins labelled with fluorescent substances.

Page 10, paragraph 3, of Akira et al. discusses a host cell comprising an expressing system that can express a receptor protein (TLR9) specifically recognizing bacterial DNA having the unmethylated CpG sequence.

Page 11, paragraph 1, of Akira et al. discusses methods for collecting and purification of a receptor protein (TLR9), including affinity chromatography via an antibody bound to a column matrix.

Page 18, paragraphs 1-2, of Akira et al. discuss kits comprising wt TLR9 for diagnosing individuals with a mutated TLR9 protein.

Page 19, lines 1-17 discuss a probe that is whole or part of an antisense chain of DNA (cDNA) or RNA (cRNA) encoding a receptor protein (TLR9).

As provided by the cited sections of the June 29, 2011 Office Action, Akira et al. fails to disclose, teach or suggest with any particularity the claimed protein (25% to 35% homology of the wild type CGBP protein) of the presently claimed invention. Instead, it is apparent from considering Akira et al. as a whole that the subject matter of the receptor protein is directed to TLR9. Considering the complete disconnect between the presently claimed invention and the subject matter disclosed in Akira et al., Applicants respectfully submit the June 29, 2011 fails to establish a *prima facie* case of anticipation. At least for these reasons, Applicants respectfully request reconsideration and withdrawal of the rejections of independent claims 1 and 27 and their respective dependent claims.

Rejected Dependent Claims

Dependent claim 3 recites "wherein the protein is capable of recognizing non-methylated CpG motifs." Since claim 3 depends from independent claim 1, the term "the protein" refers to

"a protein which specifically binds prokaryotic DNA and has 25% to 35% homology with the wild type CGBP protein." As provided above, Akira et al. fails to disclose, teach or suggest with any particularity the claimed protein (25% to 35% homology of the wild type CGBP protein) of the presently claimed invention. Instead, it is apparent from considering Akira et al. as a whole that the subject matter of the receptor protein is directed to TLR9. Indeed, nowhere does Akira et al. teach, disclose, or suggest a protein which has 25% to 35% homology of the wild type CGBP protein being capable of recognizing non-methylated CpG motifs. At least for this reason, Applicants respectfully submit dependent claim 3 is allowable.

Dependent claim 4 recites "wherein separation is followed by a step for separating the DNA from the protein of the complex." The June 29, 2011 Office Action generally cites page 10, paragraphs 2-3, page 11, paragraph 1, page 18, paragraphs 1-2, and page 19, lines 1-17. However, nowhere in any of these cited passages is this claim limitation disclosed, taught, or suggested. At least for this reason, Applicants respectfully submit dependent claim 4 is allowable.

Dependent claims 5-7, 10-11 and 14 are generally directed to the immobilization of the protein having 25% to 35% homology of the wild type CGBP protein bound to a carrier, the carrier itself, and the way the protei is bound to the carrier. The June 29, 2011 Office Action generally cites page 27, claim 23, page 10, paragraphs 2-3, page 11, paragraph 1, page 18, paragraph 1-2, and page 19, lines 1-17. Applicants have carefully studied Akira et al. and there does not appear to be any disclosure, teaching or suggestion regarding the immobilization of the protein having 25% to 35% homology of the wild type CGBP protein to be used for DNA

enrichment in the cited passages. At least for these reasons, Applicants respectfully submit dependent claims 5-7, 10-11 and 14 are allowable.

Dependent claim 13 recites "wherein separation is effected by means of electrophoresis." The June 29, 2011 Office Action generally cites page 11, paragraph 1. Applicants have carefully studied this passage of Akira et al. and do not find any mention of electrophoresis. At least for this reason, Applicants respectfully submit dependent claim 13 is allowable.

Dependent claim 15 recites "wherein the solution contains a mixture of eukaryotic and prokaryotic DNA" and dependent claim 16 recites "wherein the prokaryotic DNA is bacterial DNA." The June 29, 2011 Office Action generally cites the Abstract, page 27, claim 23, page 10, paragraphs 2-3, and page 18, paragraphs 1-2. Applicants have carefully studied these passages of Akira et al. and do not find either of these claim limitations. Thus, Applicants respectfully submit dependent claims 15 and 16 are allowable.

Dependent claims 17 and 26 pertain to the solution being a body fluid or is derived therefrom. The June 29, 2011 Office Action cites page 18, paragraph 1 for the proposition of Akira et al. teaching the solution is derived from body fluid and comprises cell preparation from blood, saliva, urine. As already discussed above, this passage discusses kits comprising wt TLR9 for diagnosing individuals with a mutated TLR9 protein. The sequence of wt TLR9 may be compared with the sequence of an individual suspected to have a mutated TLR9 DNA, which may be isolated from a body fluid. However, this disclosure of Akira et al. has nothing to do with the subject matter as presently provided in claims 17 and 26, which cannot properly be considered independently of the subject matter of independent claim 1 - the protein having 25%

to 35% homology of the wild type CGBP protein. At least for this reason, Applicants respectfully submit dependent claims 17 and 26 are allowable.

The June 29, 2011 Office Action rejected claims 18 and 19 stating Akira et al. teaches on page 11, paragraph 1, that the separation is achieved by means of a filter matrix (column) upon which the protein is immobilized. Applicants respectfully disagree. This cited passage of Akira et al. only discloses the isolation of the receptor protein, namely TLR9, and fails to disclose, teach or suggest the separation of any protein-DNA complex, much less the presently claimed protein-DNA complex. At least for this reason, Applicants respectfully submit dependent claims 18 and 19 are allowable.

Dependent claim 21 recites "wherein after step b) the prokaryotic DNA is amplified in a step c)." The June 29, 2011 Office Action states Akira et al. teaches that the DNA is amplified, citing page 18, paragraph 1. This cited passage of Akira et al. discloses that the DNA of an individual suspected of having a mutated TLR9 gene may be amplified before the comparison with the wt TLR9 sequence. This does by no means anticipate the subject matter of dependent claim 21, wherein the prokaryotic DNA is amplified following the separation of the protein-DNA complex step. At least for this reason, Applicants respectfully submit dependent claim 21 is allowable.

The June 29, 2011 Office Action rejected claims 28-29 stating Akira et al. teaches diagnosis of cancer having specific methylation pattern on page 15, paragraph 1. Applicants respectfully disagree. This cited passage of Akira et al. specifically is directed to diseases or the like caused by the deletion or abnormality of TLR9 activity. At least for this reason, Applicants respectfully submit dependent claims 28 and 29 are allowable.

As provided by the foregoing, Akira et al. fails to disclose, teach or suggest with any particularity the claimed limitations, which pertain to the protein (25% to 35% homology of the wild type CGBP protein) of the presently claimed invention. Instead, it is apparent from considering Akira et al. as a whole that the subject matter of the receptor protein is directed to TLR9. Considering the complete disconnect between the presently claimed invention and the subject matter disclosed in Akira et al., Applicants respectfully submit the June 29, 2011 fails to establish a *prima facie* case of anticipation for any of the foregoing dependent claims. Instead, it is apparent that the Examiner has improperly picked and chose features disclosed in an entirely different context. At least for these reasons, Applicants also respectfully request reconsideration and withdrawal of the rejections of dependent 3-7, 10-19, 21, 22-23, 26, and 28-29.

Additional Comments Regarding Akira et al.

As presently claimed in independent claims 1 and 27, the object of the present invention is to provide a robust and sensitive in vitro method for the separation and/or enrichment of prokaryotic DNA (claim 1) and non-methylated DNA in the presence of methylated DNA (claim 27), which is achieved according to the respective steps of the independent claims with a protein having 25% to 35% homology of the wild type CGBP protein.

In stark contrast, "[t]he goal of [Akira et al.] is to provide a receptor protein TLR9, member of the TLR family specifically recognizing bacterial DNA comprising an unmethylated CpG sequence, the DNA encoding it, and the artificial animal models useful in examining response of host immune cells to bacterial infectious diseases, which elucidate effects of oligonucleotides comprising an unmethylated CpG sequence of bacterial DNA at the molecular

level." (Page 2 at full ¶ 2.) The ability of TLR9 of binding non-methylated DNA has long been known and is acknowledged by Applicants.

Coincidentally, Akira et al. and the presently claimed invention both mention proteins binding non-methylated DNA. However, the respective objects of the presently claimed invention and Akira et al. are fundamentally different. Also, the protein having 25% to 35% homology of the wild type CGBP protein is not suggested by Akira et al. As such, a person of ordinary skill in the art would not search for a solution of the object of the present invention and turn towards the disclosure of Akira et al. to achieve the presently claimed invention. Indeed, the protein having 25% to 35% homology of the wild type CGBP protein of the present invention is a completely different protein than that disclosed in Akira et al. Based upon the protein claimed in independent claims 1 and 27, Applicants have developed a robust and sensitive in vitro method for the separation and/or enrichment of non-methylatd DNA in the presence of methylated DNA or prokaryotic DNA as presently claimed.

One of ordinary skill in the art knows that the transfer of an in vivo principle to an in vitro method is not straightforward and in most cases requires novel features. Thus, to transfer an in vivo method using a specific protein to an in vitro method using a completely different protein is even farther afield, which is the case regarding the presently claimed invention and Akira et al. Thus, when properly considered in its entirety (i.e., as a whole), Akira et al. there is no reasonable basis to conclude that one of ordinary skill in the art would modify Akira et al. to read on the presently claimed invention.

Additional Comments Regarding Claims 2 and 8-9

In the December 17, 2010 Office Action, dependent claim 2 was identified as containing allowable subject matter and would be allowable if rewritten in independent form including all of the limitations of the base claim. Although Applicants overcame the previous rejection and new grounds for rejection were forwarded in the June 29, 2011 Office Action, dependent claim 2 was not rejected on its merits over any prior art. Instead, dependent claim 2 was provisionally rejected on the grounds of non-statutory obviousness-type double patenting as being unpatentable over claims 1-16 of co-pending Application No. 10/528,235.

Likewise, dependent claims 8-9 were not rejected on its merits over any prior art. Instead, dependent claims 8-9 were also rejected under the double patenting rejection concerning the '235 application.

While Applicants respectfully traverse the double patenting rejection as provided below, Applicants respectfully request the subject matter of dependent claims 2 and 8-9 be identified as being allowable.

Double Patenting Rejection

The June 29, 2011 Office Action provisionally rejected claims 1-19, 21-23 and 26-29 on the grounds of nonstatutory obviousness-type double patenting as being unpatenable over claims 1-16 of co-pending Application No. 10/528,235. While pending claims 1-10 and 12-20 (renumbered 1-19 respectively) of the '235 application have been identified as being allowable in the June 27, 2011 Notice of Allowance, such claims have not yet issued. Accordingly, the provisional rejection is premature. Nonetheless, Applicants respectfully traverse this rejection.

While the June 29, 2011 Office Action admits the alleged conflicting claims are not identical, it is asserted "they are not patentably distinct from each other because the claim 1, 23, 25-27 are ***generic*** to all that is recited in claims 1-2, 15-16 of the co-pending application '235. That is, claims 1, 23, 25-27 are anticipated by the claims 1-2, 15-16 of the co-pending application '235. Specifically the method of enriching prokaryotic DNA by contacting said DNA with a polypeptide or protein that specifically binds to said protein and separating or isolation, enriching the complex of protein-DNA, are within the scope of the patented claims....The courts have stated that a genus is obvious in view of the teachings of a species." (O.A. at p. 5 (emphasis added).)

The Genus/Species Requirement is NOT Present

As provided in the June 29, 2011 Office Action and relied upon by the Examiner, courts have stated that a *genus* is obvious in view of the teachings of a *species*. Thus, in this situation, the genus must be the instant application and the species being the '235 application. Such, however, cannot possibly be the case.

Independent claims 1 and 27 of the present application are directed at a method of separating and/or enriching prokaryotic DNA (claim 1) and non-methylated DNA (claim 23) by contacting at least one prokaryotic DNA with a protein having 25% to 35% homology of the wild type CGBP protein. Meanwhile, claims 1-2, 15-15 of the co-pending application '235, include contacting at least one procaryotic DNA with at least one protein or polypeptide which is specifically capable of specifically binding to the procaryotic DNA. As provided by the foregoing, the specific protein of the present invention cannot possibly be a genus with the general protein of the '235 application being a species. Accordingly, the provisional double

patenting rejection is improper, and Applicants respectfully request reconsideration and withdrawal of said double patenting rejections.

Conclusion

In view of the foregoing, it is submitted that this application is in condition for allowance. Favorable consideration and prompt allowance of the application are respectfully requested.

The Examiner is invited to telephone the undersigned if the Examiner believes it would be useful to advance prosecution.

Respectfully submitted,

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